02-C-0259: Pilot Study of Allogeneic Blood Stem Cell Transplantation in Patients with High-Risk and Recurrent Pediatric Sarcomas

This protocol is allogeneic PBSCT transplant in patients with matched first degree related donors for high-risk pediatric sarcomas. Endpoints will be feasibility and toxicity of this approach as well as evaluation for any evidence of graft vs. tumor effects. This protocol will also provide a platform for the future development of tumor-specific vaccines that could be administered following allogeneic PBSCT in an attempt to specifically direct graft versus-tumor responses toward pediatric sarcomas.

ELIGIBILITY CRITERIA:

Diagnosis: The following diagnoses will be considered:

- Patients who present at the time of initial diagnosis with macrometastatic disease (except patients with Ewing's sarcoma metastatic to lung only) may be enrolled after completion of standard front-line therapy. Standard front line therapy for alveolar rhabdomyosarcoma should include vincristine and cyclophosphamide, plus actinomycin D and/or adriamycin. For patients with Ewings' sarcoma, standard front line therapy should include vincristine, cyclophosphamide, adriamycin, ifosfamide and etoposide.
- Patients with recurrence of tumor at any site less than one year after completing standard front-line therapy or with a second or subsequent recurrence at any time after completing standard front-line therapy.
- Patients with progression of disease while receiving standard front-line chemotherapy who cannot achieve a CR with local treatment modalities

b) The following patients with desmoplastic small round cell tumor are eligible after receiving front line standard therapy, which is defined as a regimen containing at least vincristine, cyclophosphamide, and adriamycin:

- unresectable disease
- metastatic tumor (abdominal and extra-abdominal disease)
- progressive while receiving standard therapy
- recurrence within one year of completing therapy

Patients without evaluable tumor at the time of enrollment are eligible

Prior Therapy: Patients who have previously received high-dose chemotherapy with autologous stem cell rescue are eligible for this trial at a minimum of 8 weeks after completion of autologous BMT.

Age: Patient age of >4 years and <30 years at diagnosis and age < 35 years of age. Availability of a 5 or 6 antigen HLA-matched first-degree relative donor (single HLA-A or B mismatch allowed). Genotypically identical twins may serve as stem cell donors. Genotypic identity must be confirmed by RFLP analysis.

Performance Status: ECOG performance status of 0, 1, or 2 or, for children≤10 years of age, Lansky≥60(Appendix A).

Life expectancy: >3 months.

Cardiac function: Left ventricular ejection fraction ≥45% by MUGA or fractional shortening ≥28%.

Pulmonary function: DLCO ≥50% of the expected value.

Renal function: Age-adjusted normal serum creatinine according to the following table or a creatinine clearance ≥ 60 ml/min/1.73 m2.

Age (years)	Maximum serum creatinine (mg/dl)
≤5	0.8
>5, ≤ 10	1.0
>10, ≤15	1.2

>15	1.5

Liver function: Serum total bilirubin < 2 mg/dl, serum AST and ALT ≤2.5 x upper limit of normal.

Marrow function: ANC must be > 750/mm3 (unless due to underlying disease in which case there is no grade restriction), platelet count must be ≥ 75,000/mm3 (not achieved by transfusion) unless due to underlying disease in which case there is no grade restriction).

Lymphopenia, CD4 lymphopenia, leukopenia, and anemia will not render patients ineligible.

Informed Consent: Ability to give informed consent. For patients<18 years of age their legal guardian must give informed consent. Pediatric patients will be included in age appropriate discussion in order to obtain verbal assent.

Durable power of attorney: form completed (patients≥18 years of age only).

INCLUSION CRITERIA: DONOR

- Weight ≥ 15 kilograms.
- First degree relative with genotypic identity at 5 or 6 HLA loci (single HLA-A or B locus mismatch allowed). Genotypically identical twins may serve as stem cell donors. Genotypic identity must be confirmed by RFLP analysis.
- For donors <18 years of age, he/she must be the oldest suitable donor, their legal guardian must give informed consent, the donor must give verbal assent, and he/she must be cleared by social work and a mental health specialist to participate.
- For donors ≥ 18 years of age, ability to give informed consent.
- Adequate peripheral venous access for apheresis or consent to use a temporary central venous catheter for apheresis.
- Donor selection criteria will be in accordance with NIH/CC Department of Transfusion Medicine standards.

EXCLUSION CRITERIA: PATIENT

- Active fungal infection.
- History of CNS tumor involvement. Extradural masses which have not invaded the brain parenchyma (as is commonly observed in Ewing's sarcoma family of tumors) or parameningeal tumors (as is commonly observed in rhabdomyosarcoma) without evidence for leptomeningeal spread will not render the patient ineligible.
- Lactating or pregnant females.
- HIV positive (due to unacceptable risk following allogeneic transplantation).
- Hepatitis B surface antigen (HBsAg) positive or hepatitis C antibody positive with elevated liver transaminases. All patients with chronic active hepatitis (including those on treatment) are ineligible.
- High risk of inability to comply with transplant protocol, or inability to give appropriate informed consent in the estimation of the PI, social work, or the stem cell transplant team.
- Fanconi Anemia

EXCLUSION CRITERIA: DONOR

- History of medical illness which poses a risk to donation in the estimation of the PI or the Department of Transfusion Medicine physician including, but not limited to stroke, hypertension that is not controlled with medication, or heart disease. Individuals with symptomatic angina or a history of coronary bypass

grafting or angioplasty will not be eligible.

- History of congenital hematologic, immunologic, oncologic or metabolic disorder, which poses a prohibitive risk to the recipient in the estimation of the PI.
- Anemia (Hb less than 11 gm/dl) or thrombocytopenia (< 100,000/μl).
- Lactating or pregnant females. Donors of childbearing potential must use an effective method of contraception during the time they are receiving G-CSF. The effects of cytokine administration on a fetus are unknown and may be potentially harmful. The effects upon breast milk are also unknown and may potentially be harmful to the infant.
- HIV-positive, hepatitis B surface antigen (HBsAg) positive or hepatitis C antibody positive. Donors are providing an allogeneic blood product and there is the potential risk of transmitting these viral illnesses to the recipient.
- High risk of inability to comply with transplant protocol.

PRETREATMENT EVALUATION:

- All must be completed within 4 weeks of study entry

Clinical:

- All patients and donors will be screened by complete medical history and physical examination.
- Donors will complete a Blood Bank screening questionnaire in the Department of Transfusion Medicine (DTM).
- Dental consultation to assess need for teeth cleaning, caries correction or extraction (patient only).
- Social work consultation (patient and donor).
- Durable power of attorney form completed (patients ≥ 18 years of age).
- Donors who are minors will be evaluated by a mental health specialist with pediatric expertise (psychologist or psychiatrist) prior to the assent process to determine willingness to participate (donors < 18 years of age only).
- Laboratory Serologic Evaluations: (patient only, unless specified)
- Typing for HLA-A, -B, or -DR performed in at the NIH DTM (donor and patient). HLA typing may be performed at any time prior to entry without time limitation.
- Blood type, screen, and, if blood type identical, RBC phenotyping, must be performed at the NIH DTM laboratory (donor and patient). In cases of major ABO incompatibility isohemagglutinin titers must be performed. Typing may be performed at any time prior to entry without time limitation.
- Bilateral bone marrow aspirates and biopsies (for patients with a prior history of bone marrow involvement only).
- Spinal fluid for cell count and cytology (for patients with a history of parameningeal alveolar rhabdomyosarcoma).
- Variable number tandem repeat (PCR) analysis of DNA mini-satellite regions for future determinations of chimerism (donor and patient).
- Infectious disease testing per Blood Bank standards to include HIV, HTLV, HBV, HCV, CMV, and syphilis (patient and donor). Donor testing will be performed no more than 30 days prior to each collection.
- Antibody screen for varicella, HSV, and toxoplasma (patient only) and EBV (patient and donor).
- PPD with appropriate control (for patients considered to be at high risk).

- CBC with differential (patient and donor). Must be repeated within 72 hours of first collection and within 24 hours of subsequent collections (donor).
- Electrolytes, glucose, BUN, creatinine, AST, ALT, alkaline phosphatase, bilirubin, urinalysis, protime, partial thromboplastin time (patient and donor).
- Calcium, magnesium, phosphorus, uric acid, lactate dehydrogenase (LDH).
- Urine •HCG in post-pubertal females (patient and donor).
- Serum iron, ferritin and TIBC.
- 24-hour urine for creatinine clearance.
- Spot urine for calcium/creatinine ratio.

Radiologic, Nuclear Medicine, and Specialty Studies:

- Chest radiographs.
- CT scans of the chest, abdomen and pelvis and primary tumor.
- MRI scans of the head and primary tumor.
- Technetium99m bone imaging.
- Pulmonary function tests (vital capacity, FEV-1, DLCO).
- Electrocardiogram and MUGA scan or ECHO.
- All radiologic studies that measure identifiable disease will be repeated prior to each cycle of immune depleting chemotherapy and prior to the conditioning regimen.

Pathologic/Tissue Evaluation:

- All tissue will be reviewed by the NCI Department of Pathology and the diagnosis must be confirmed prior to enrollment.

GENERAL TREATMENT PLAN: TREATMENT SCHEMA

Donor: Peripheral Blood Stem Cell Harvest:

- Filgrastim mobilization, 10 μg/kg per day SQ for 5-7 days until collection completed
- Stem cell apheresis
- Stem cell cryopreservation

Patient:

- Fludarabine-EPOCH Induction Chemotherapy
- 1 to 3 cycles; 21 d cycles; Cycles 2 and 3 may dose-modified.
- Fludarabine, 30 minutes daily for 3 days; days 1-3
- Etoposide, continuous IV infusion daily for 4 days; days 1-4
- Doxorubicin, continuous IV infusion daily for 4 days; days 1-4
- Vincristine, continuous IV infusion daily for 4 days; days 1-4
- Cyclophosphamide, IV over 30 minutes; day 5
- Prednisone, daily in 2-4 divided doses PO for 5 days; days 1-5
- Filgrastim, dailySQ from day 6 until ANC >1000/μl x 2 days
  - Stem Cell Infusion
  - Transplant Day 0 : stem cells by IV infusion
- Filgrastim, SQ from day 0 until ANC >5000/μl x 3 days
  - GVHD Prophylaxis
- Cyclosporine-A: Begin day -1, titrate to maintain a trough level of 150-300 ng/ml. For patients with genotypically identical twins as stem cell donors, no cyclosporin will be used.
  - Pre-BMT Preparative Chemotherapy

- Transplant Days -6 to -3
- Fludarabine, IV over 30 minutes daily for 4 days; days -6, -5, -4, -3 of transplant
- Cyclophosphamide, IV over 2 hours daily for 4 days; days -6, -5, -4, -3 of transplant
- Mephalan, IV infusion over 1 hour for 1 day; day -2 of transplant
- Mesna, continuous IV infusion daily for 4 days; days -6, -5, -4, -3.
- Day 0 – infusion of donor stem cells

RESEARCH STUDIES: Cyclosporine, host immune depletion and reconstitution chimerisms, and IL-7 monitoring.

HOSPITALIZATION: Induction chemotherapy can be done as an outpatient. Transplantation requires hospitalization.

ACCRUAL: Open to accrual. A total of 28 – 31 donors and 28 –31 recipients will be accrued.